ORGANISMAL DIFFERENTIALS AND ORGAN DIFFERENTIALS

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A series of transplantations of normal tissues and tumors which began in 1895, and was continued for a period of approximately fifty years, led to the concept that among various other substances functioning in a vertebrate organism, there is present in all, or almost all the tissues of an individual, among the higher organisms, a system of chemical substances, which is identical in the organs and tissues of the same individual, and which differs from that present in any other individual. In this system there is one particular substance which characterizes an individual, in contrast to a larger unit, such as a species. This chemical substance characteristic of an individual has been designated as his individuality differential. The character of the individuality differential is determined by and representative of the set of nuclear genes of this individual. The similarity and compatibility between the individuality differentials of the various individuals belonging to the same species depends upon the genetic relationship between these individuals. The pedigree relationship between members of a certain family also depends upon, and is an indicator of their genetic relationships, and in the analysis of genetic relationships, we may make use of family relationship and of phylogenetic relationships in general. In addition to the individuality differentials, there are present in each individual substances characterizing strains, races, species, genera and classes. Such a set of various substances represents the organismal differentials of an individual, or of a species.[1]

The individuality differential of an individual functions as an autogenous substance. The individuality differentials of other individuals in this species show different degrees of relationship to the first individual and and his differential. The individuality differentials of strange, not nearly related individuals, especially if they belong to a different strain, are homoiogenous in their relation to the first individual. Nearly related individuals belonging to the same family are characterized by syngenesious individuality differentials in their relationship to the first individual. The average of the syngenesio-differentials is more similar to the first individuality differential than is the average of the homoiogenous differentials, but within these various ranges (e. g., the syngensio-range) some special relationships exist according to the position in the family tree which these various individuals occupy.

A piece of normal tissue or tumor, when introduced into a host possessing a strange individuality differential, calls forth antagonistic reactions on the part of various types of host cells; the most characteristic of these is the

reaction of the lymphocytes of the host, which quantitatively indicates the degree of nearness or distance in the genetic relationship between host and transplant. It is the host which reacts against the transplant. Besides the lymphocytes, the connective tissue cells and blood vessels of the host react against bearers of strange individuality differentials. Furthermore, immune substances, which seem to be carried by the blood serum of the host, and, in all probability, also preformed substances present in the blood serum, may act against the strange organismal differentials. If the genetic relationship between host and transplant is as distant as that between two species or between distinct subspecies, a reaction on the part of polymorphonuclear leukocytes of the host partly replaces that of the lymphocytes. The mode and intensity of the reaction of the host cells is ultimately determined by the genes in the transplant, which are not represented in the host and are therefore strange to him. The reactions of a host are different if a piece of tissue from a hybrid offspring is introduced into one of the parents and if a piece from one of the parents is introduced into the hybrid offspring, a difference which was recognized in our early experiments. Notwithstanding these differences in the reactions in particular cases, it is justifiable to distinguish between the syngenesious and the homoiogenous relationship because both are characterized by different averages and by a different site in the spectrum of genetic relationships.

If families within the same species are continuously bred separately from one another, different strains develop. If the inbreeding in such families becomes very close as a result of continuous brother to sister mating, the individuals belong to such a strain may become more and more similar to one another in genetic constitution, although, contrary to the usual assumption, it seems to be very difficult to produce absolute identity between the individual differentials of the various members of a closely inbred strain.

In contrast to the organismal differentials which are the same in the different parts of an organism, we must distinguish the differentials of the various organs and tissues. Organs and tissues of an individual, though possessing the same organismal differentials, possess different organ and tissue differentials, based on their specific structure, metabolism and function, and especially on specific substances present intracellularly or given off to the surrounding body fluids. These organ and tissue differentials are very similar in different individuals; for example, the kidney and thyroid differential in one individual is very similar to the same organ differential in another individual. The organ and tissue differentials can be transferred either to a different site in the same individual or to a different individual, apparently without calling forth antagonistic reactions on the part of the host, except that under certain conditions immune reactions can also be produced against organs. Reactions which take place after transfer to a strange in-

dividual as a rule must be attributed to the strange organismal differentials which are associated with the organs and tissues. Thus, homoiotransplanted pieces of kidney and thyroid, although each differs greatly as to the organ-tissue differentials from the other, may elicit similar antagonistic reactions on the part of the host. However, the organ differentials may modify the action of the homoiogenous individuality differentials by influencing the cellularity and perhaps the activity of the metabolic processes of the transplant and thus they may influence the amounts of organismal differentials which are produced by the transplant and they may also affect the ready elimination of the organismal differentials and their action on the host; accordingly it might be expected that cartilagenous intercellular substances would be unfavorable to the ready discharge of the organismal differentials; moreover differences in the structure of the transplant might modify the resistance of the transplant to the antagonistic actions of the host. The organ-tissue differentials are also controlled by genes; but they are not identical with the genes which control the individuality differentials.

Organismal and organ-tissue differentials resemble each other in that both have undergone a phylogenetic as well as ontogenetic development; they both have progressed in a parallel way from simple to complex formations, ontogenetically and phylogenetically. However, this development took place in a somewhat different manner in these two types of differentials. The various organ-tissue differentials (e. g., those of kidney, thyroid, skin and liver) vary in different individuals, strains and species within a certain range independently of one another, and independently also of the organismal differentials associated with them.

Both organismal differentials and organ-tissue differentials have distinctive fields of function. In general, it is the function of the organismal differentials to maintain the integrity of the individual which they represent, to protect it against strange organisms or their component parts, against strange individuality differentials. At the same time, the identity of the individuality differentials and their autogenous nature, within the the same individual, prevent antagonistic reactions against the various constituents of its own body and makes them function as a harmonious whole. At least this is true as long as the different constituents of the body are approximately normal. Against strange individuality differentials the invaded host defends himself by means of the cellular reactions which take place around the strange material and presumably also by means of his own body fluids, at least under certain conditions. Strange organismal differentials serve readily as antigens and accordingly call forth the production of immune reactions. The initiation of immunity is therefore an important function of the organismal differentials. These reactions are the stronger the more distant the organismal differentials of the host are

from those of the invading organism; they are stronger against the bearers of strange species differentials than against the bearers of homoiogenous individuality differentials. It is therefore by means of strange organismal differentials serving as antigens that immunization against transplanted pieces of tumor possessing a different organismal differential is achieved. However, it is possible that, if the strength of the immunity produced differs in case different organs are used as antigens for the immunization of the host, organ-tissue differentials may play an additional role as antigens.

Early investigations on transplantation of tumors proved the existence of immune reactions against the strange organismal differentials which they carried, and we also noted the development of immunity against transplanted tumors which were bearers of individuality differentials differing from those of the host. We believed that similar immunizations might be expected to develop also against transplants of normal tissues which carried strange individuality differentials, but our early attempts to prove the existence of such immune or sensitizing reactions by means of the lymphocytic reaction did not yield a positive result; a second transplantation into a host which should have been immune as the result of a preceding transplantation of related tissue was not followed by an earlier or more intense lymphocytic reaction. However, subsequent experiments carried out in our laboratory by H. T. Blumenthal[2] proved that a second transplantation of normal tissue led to an earlier appearance of lymphocytes in the blood, although the number of lymphocytes was not increased. The immune reaction was therefore weak, and this suggested that the body fluids might also participate in the injury of the transplant by means of preformed substances which they carried. The recent experiments of Kidd[3] showed that immunity against transplanted Brown-Pearce carcinoma in the rabbit depends upon immune substances developing in lymphoid organs and that the immunized lymphocytes injured by direct action the strange tumor cells; on the other hand, in the blood serum of the host, the presence of immune substances could not be demonstrated. This latter observation is in agreement with the negative results of earlier attempts to demonstrate the presence of antibodies against strange transplanted tumor in the blood serum. The experiments of Kidd were carried out with homoiogenous tumor. It is conceivable that immunization against different species might permit the observation of antibodies also in the blood serum of the host.

Very different from the functions of the organismal differentials are those of the organ-tissue differentials. The latter as such and in their interaction which other organs make possible the normal life of the individual and its principal pathological deviations. In particular, they are also responsible for the reproductive processes of the individual and for his psychical manifestations which latter are dependent on the function of the nervous system within the whole organism. There is ordinarily an interaction between

the organ and tissue specificities and various environmental factors. By means of the psychical processes, the individual creates a picture of his personality which he attempts to elevate in the social struggle with other individuals. The psychical individuality differs from that essentially based on the function of the organismal differentials in that the former is amenable to the influence of psychical factors, such as thoughts, emotions and suggestions.

Likewise, various abnormal phenomena, such as growth processes, and in particular the development of tumors are the expression of changed organ functions; and although these changes may vary in accordance with differences in genetic relationships of individuals, strains, and species, they are not essentially the expression of organismal, but of organ differentials, which latter vary in accordance with family, strain, species characteristics. Also, various reactions of cancerous tissue are the expression of the organ-tissue differentials of the cancer or of the tissue from which it originated.

As the result of close inbreeding by consecutive brother to sister matings in families belonging to the same species, all individuals belonging to the strains thus developing become more and more similar, without, however, as a rule reaching identity in their genetic constitution and a completely autogenous state. The increasing similarity resulting from close inbreeding applies to both organismal differentials and organ-tissue differentials. If matings were not limited to brothers and sisters, but took place also between less nearly related individuals, the homogeneity in the reactions of the members of such families became less great; but the reactions in closely inbred families and in less closely inbred families differed only in degree and various intermediate stages did develop. It has therefore been possible to recognize some of the important characteristics of tumors and also of normal tissues in the course of the early study of animals affected by cancer preceding the time when very closely inbred strains were available for research; these characteristics may serve as examples for various other kinds of reactions that may take place under such conditions. Thus as far as the organismal differentials are concerned, it was recognized at these early periods that the lymphocytic reaction corresponds to the genetic relationship between host and transplant and to the relationship of their individuality differentials. This implies that the genetic constitutions of both host and transplant (donor) control the reactions of the host.[1]

Furthermore, the reactions of the host were found to be more severe when tissues of the hybrid offspring were transplanted into the parents than when tissues of the parents were transplanted into the offspring. Likewise, the theory of the individuality differentials implied, and it was subsequently also stated by Loeb and Wright[4] that the reaction of the host against the transplant does not depend upon the presence of a given number of factors in the transplant, but that the host reacts against the genes strange to him

which are present in the transplant. In addition it was noticed in this early period that successive transplantations of pieces of tumor within the same species as a rule increased the growth energy and decreased the latent period of the transplant.[5] We attributed this effect to mechanical stimulation of the transplant which occurred during the process of transplantation rather than to a loss of genes in the transplant; no change in the constitution of the individuality differential of the latter was involved.

Our early observations also noted the preponderance of the influence on the mother in the development of mammary carcinoma in the hybrid offspring in mice, if both parents differed in their genetic tendency in respect to the formation of this tumor.[6] In the case of mammary cancer of mice it was likewise established at this time that its appearance does not depend solely upon the nature of the organ-tissue differential in an individual belonging to a certain strain, but upon the interaction of this differential with hormones and it was suggested that a similar interaction between organ differentials and hormones might apply also in the case of abnormal growth processes in other organs.[7] In a few cases in which surgeons had unsuccessfully attempted to treat mammary carcinoma in patients by ovariectomy, no thought seems to have been involved as to the important role which hormones may play in the origin of cancer.

We may briefly mention some other observations made at this early period when not yet closely inbred strains were used in the transplantation of normal tissues or tumors, and in the experimental study of the development of cancer in certain organs. Thus, we observed the relationship between the incidence of tumors and the length of the latent period in the formation of mammary carcinoma in mice.[8] Likewise the action of multiple factors in the transplantation of tissues and in the development of tumors was recognized, the occurrence of many intermediate degrees of tumor incidence in certain families and strains was established, and the effect of breeding and pregnancies in increasing the incidence of mammary carcinoma in mice and the occurrence of variations in the strength of this influence in different strains also was noted.[1, 9] Observations were made concerning the effects of hybridization on the tumor incidence and concerning a possible relationship between hair color and the incidence of tumors. It was also noted that animals bearing a spontaneous tumor were a more favorable soil for transplantation of another spontaneous tumor that had developed in a homoiogenous animal.[10] The occurrence of a competitive struggle between adjoining tissues if they are affected by certain stimulations, either hormonal or mechanical, was also recorded at this time.[11]

During the process of close inbreeding of a strain, the sets of genes of the different members of the strain change from unlikeness more and more in the direction toward identity of distribution and in accordance with this change in the assortment of genes the reactions of the different organisms composing

the strain and of their constituent organs and tissues also undergo changes and become more and more alike in the different members of the strain. These changes in the individuals and in the various reactions of the organs of these individuals presumably take place at different stages in this process of inbreeding. The results observed depend also on the degree of relationship of these characteristics to factors in the inner or outer environment. The more these changes depend on environmental factors, the less readily do the reactions among different individuals tend to become identical, and it is merely the averages in the modes of reaction which approach identity. On the whole in their development the organismal differentials seem to be more independent of the environment than are various organ and tissue differentials, which may interact not only with variable environmental factors, but also with the organismal differentials. Thus, whereas in a closely inbred strain, the organismal differentials may approach identity in the various individuals as shown by transplantation experiments, the reactions of various organs as those of the mammary gland may vary greatly in individuals belonging to the same strain, as indicated by the individual variations in the development of tumors and in some of the other reactions which we mentioned.[8] In these cases only the averages in the reactions of the organs may become increasingly alike in the various individuals of the inbred strain. Therefore, with the continued progress in inbreeding, the similarity in the reactions which depend on the organismal differentials becomes increasingly greater until in the end they approach identity in different individuals, in contrast to the reactions which depend on organ-tissue differentials when the individual variations may remain greater.

It will be the task of further investigations to continue the study of the interactions between organismal and organ-tissue differentials among themselves and with environmental factors.

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